

REMARKS**Status of the application**

Claims 1-10, 14-17, 19 and 27-33 were pending in the application, with claims 10, 14-15, 17 and 19 being withdrawn from consideration by the Examiner as directed to non-elected inventions. Claims 1-9, 16, and 27-33 are under examination and stand rejected in the instant Office Action.

With entry of the present response, claims 4, 5, 8, 29-31 and 33 have been canceled without prejudice. In addition, claims 1-3 and 16 have been amended to delete the indication of depression. Dependent claims 6-7 were accordingly amended to ensure proper claim dependency. Unless otherwise noted, the claim cancellations and amendments presented herein were intended as a further effort to facilitate prosecution of the subject application, and should not be construed as acquiescence of any ground of rejections. The following remarks are presented to address the substantive issues raised in the instant Office Action.

Mis-characterization of Fundytus et al. by the Examiner

The Examiner dismissed Applicants' arguments and Dr. Markou's declaration submitted in Applicants' previous response as not persuasive. Relying on Fundytus et al. (British J. Pharmacol. 120:1015-20, 1997), the Examiner maintained the assertion that the prior art taught that non-selective mGluR antagonist MCPG "was effective in treating withdrawal symptoms." Applicants have previously clarified that this reference reported that chronic administration of MCPG prevented the development of morphine dependence in normal rats which were simultaneously administered with morphine and the antagonist (Figure 1). Applicants further noted that Fundytus et al. also taught that, in rats already with induced morphine dependence, acute administration of mGluR antagonist including MCPG did not lead to improved withdrawal symptoms relative to controls (Figure 2).

In the instant response, the Examiner pointed to Figures 1a and 1b of Fundytus et al. for the alleged teaching that MCPG is effective in treating withdrawal symptoms. With due respect, Applicants note that the Examiner has mis-characterized the data discussed in Figures 1a and 1b of Fundytus et al. and incorrectly relied on the data in supporting the assertion of treatment of withdrawal symptoms with MCPG. As clearly explained in the "Subjects and surgery" section in Fundytus et al. (page 1016, left column), the starting rats employed in Figure 1 are normal rats which were concurrently and chronically (i.e., lasting for days) administered with morphine (to induce dependence) and a mGluR antagonist (to assess its effect on the development of dependence). After the chronic administration concludes, the rats were then examined for withdrawal symptoms in order to determine whether the rats have developed morphine dependence. Thus, Figure 1 is not concerned with mGluR antagonist treatment of rats which have already developed dependence and were then administered with the mGluR antagonists to determine their therapeutic effects on existing dependence (e.g., reducing withdrawal symptoms of dependent rats). Rats already with morphine dependence were not the starting subjects for assessing therapeutic effect of the mGluR antagonists in Figure 1. Instead, generating rats with (or without) morphine dependence by administering the different mGluR antagonists along with morphine was a means to study whether the drugs were effective in preventing the development of morphine dependence. Consistently, the measurement of withdrawal symptoms as shown in Figures 1 a and 1b was merely intended as an indicator of whether dependence was developed or prevented in rats receiving the different combination of drugs. Prior to the measurement, it was not known whether any of the rats had morphine dependence. It does not logically follow that the results shown in the figures indicate a therapeutic effect of the mGluR antagonists in rats with morphine dependence. Rather, as further clarified below, the Fundytus et al. results showed a preventive effect of the antagonist, with no efficacy in treating withdrawal if the antagonist is administered after the development of dependence.

In contrast to the chronic administration shown in Figure 1, the data reported in Figure 2 relates to acute administration of the mGluR antagonists (i.e., a single injection) to rats which have already developed morphine dependence induced via the chronic morphine administration. This is clearly explained in the following statements in Fundytus et al.:

Acute i.c.v. injections of either MCPG (n=5), MCCG (n=6) or MAP4 (n=6) were given in a dose of 2 nmol $4 \mu\text{l}^{-1}$, or 4 μl vehicle (n=15), to rats that received chronic systemic morphine treatment as described above. [page 1016, left column, last paragraph; emphasis added]

This experiment was performed to determine if acute blockade of mGluRs would decrease the expression of abstinence symptoms once dependence had developed. [page 1017, left column, second to the last paragraph; emphasis added]

The results from this study as shown in Figure 2 unequivocally indicate that none of the treatments (including treatment with MCPG) had any effect on withdrawal symptoms in morphine-dependent rats. The authors expressly note that there is **“no difference between vehicle-treated rats and mGluR antagonist-treated rats”** (page 1018, left column, 2nd and 3rd paragraphs).

In summary, Figure 1 of Fundytus et al. relates to a study which examines the effect of mGluR antagonist on preventing the development of morphine dependence in normal rats, and Figure 2 describes a different study designed to assess therapeutic effects of the mGluR antagonists in rats that have already developed dependence. The reduced withdrawal symptoms shown in Figures 1 a and 1b simply showed that, while normal rats administered with morphine and a vehicle control did develop morphine dependence, those rats treated with the mGluR antagonists along with morphine did not develop morphine dependence (or had developed less severe dependence). They do

not stand for the proposition, as the Examiner assumed, that the mGluR antagonists were effective in treating or reducing withdrawal symptoms in rats which were already determined to have morphine dependence. Instead, based on the data shown in Figure 2, Fundytus et al. concluded that the administered mGluR antagonists had no effect in reducing withdrawal symptoms in rats that have already developed dependence.

Rejection under 35 U.S.C. §103

The instant office action maintains the various obviousness rejections rendered in the previous office action. Specifically, claims 1-8, 16 and 29 remain rejected as allegedly being obvious over Adam et al. (US Patent No. 6407094) in view of Corsi et al. (US 2003/0195139) or Chiamulera et al. (Nat. Neurosci. 4:873-4, 2001), claims 9, 27, 28, 32 and 33 remain rejected as allegedly obvious over Chiamulera et al. in view of Adam et al., and claims 29-31 and 33 remain rejected as allegedly obvious over Bear et al. (US Patent No. 6916821) in view of Adam et al. Applicants have previously submitted Dr. Markou's declaration and several other references as evidence that one would not be motivated to combine a mGluR2/3 antagonist and a mGluR5 antagonist in the treatment of withdrawal symptoms. In dismissing Dr. Markou's declaration and Applicants previous arguments as not persuasive, the Examiner is apparently of the view that Fundytus et al. and the references cited by Applicants actually suggest that the claimed invention would have been obvious. Applicants respectfully traverse the rejections for the reasons already on record and the additional remarks presented below.

As an initial matter, Applicants note that claims 29-31 and 33 have been canceled. Therefore, the rejection of these claims over Bear et al. (US Patent No. 6916821) in view of Adam et al. is now moot. The following remarks are directed to the other rejections maintained in the instant office action.

First, as explained above, the Examiner's reliance on Fundytus et al. as evidence of the alleged obviousness of the present invention is clearly misplaced. Fundytus et al.

unequivocally concluded that the various mGluR antagonists, including the mGluR2/3 and mGluR5 dual antagonist MCPG, had no effect in treating withdrawal symptoms in morphine dependent rats. This reference therefore would likely lead one away from combining a mGluR2/3 antagonist and a mGluR5 antagonist as presently claimed. It certainly does not suggest that such a combination would have been obvious.

Referring to the other references cited by Applicants in the previous response, the Examiner states that these references show that “the amount of glutamate can be adjusted by adding different groups as shown by Mills et al., or by adding different receptor agonist and/antagonist as shown by Xi et al. and Thomas et al.” Applicants do not dispute that glutamate signaling can be modulated by agonists or antagonists of mGluR2/3 or mGluR5. However, this does not even remotely suggest obviousness of the present invention which relates to the combination of a mGluR2/3 antagonist and a mGluR5 antagonist in treating withdrawal symptoms. More importantly, as detailed below, the data in the references that were relied upon by the Examiner do not lend whatsoever support assumed by the Examiner in maintaining the obviousness rejection.

Specifically, Applicants previously cited Mills et al. as evidence that the art has taught that mGluR2/3 antagonist and mGluR5 antagonists can have opposing neurochemical effects on glutamate neurotransmission. In response, the Examiner asserts in the instant office action that Mills et al. also showed that Group II mGluR2/3 antagonist LY341495, but not Group II/III antagonist CPPG, potentiated the release and glutamate. Applicants do not see the relevance, if any, of these data to the issue of whether it would have been obvious to combine a mGluR2/3 and mGluR5 antagonist. This is because the data noted by the Examiner in Mills et al. only indicate the two antagonists have different activities in potentiating glutamate release. The data do not teach or suggest a combination of two antagonists of two different mGluRs, let alone showing that such a combination would be effective in treating withdrawal symptoms. In addition, unlike the presently claimed combination of a mGluR2/3 (a Group II receptor) antagonist and a mGluR5 (a Group I receptor) antagonist, the two antagonists in Mills et

al. as noted by the Examiner relate to Group II receptor and/or Group III receptor. Specifically, as acknowledged by the Examiner, LY341495 antagonizes Group II receptors such as mGluR 2 and mGluR3, and CPPG antagonizes both Group II and Group III receptors. In other words, the two mGluR antagonists noted by the Examiner, LY341495 and CPPG, do not include one that antagonizes a Group I receptor such as the presently recited mGluR5 antagonist. Thus, the reference to Mills et al. by the Examiner by no means negate that fact that mGluR2/3 antagonists and mGluR5 antagonists can have opposing neurochemical effects on glutamate neurotransmission. It certainly does not suggest that the presently claimed combination would have been obvious.

Similarly, Applicants have previously cited Xi et al. (J. Pharmacol. Exp. Ther. 300:162-71, 2002), Thomas et al. (Neuropharmacology 41: 523-7 2001) and de Novellis et al. (Eur J Pharmacol 462: 73-81 2003) to show that it is known in the art that mGluR2/3 antagonist LY143495 increased extracellular glutamate in the nucleus accumbent, and that the mGluR5 antagonist MPEP inhibited glutamate release in vitro and in vivo in the corpus striatum. In response, the Examiner notes that Xi et al. also found that the mGluR2/3 antagonist LY341495 when combined with mGluR2/3 agonist APDC decreased glutamate release. Again, Applicants are puzzled by the Examiner's statement. Applicants fail to see the relevance of these data to the non-obviousness nature of the present invention. This is because the combination of a mGluR2/3 antagonist and a mGluR2/3 agonist in Xi et al., as noted by the Examiner, is simply irrelevant to the issue of combining a mGluR2/3 antagonist and a mGluR5 antagonist. Applicants' invention is not directed to a combination of a mGluR2/3 antagonist and a mGluR2/3 agonist. Rather, the presently claimed invention is directed to the combination of a mGluR2/3 antagonist and a mGluR5 antagonist. Applicants respectfully request a clarification from the Examiner if the Examiner chooses to maintain this aspect of the rejection.

Applicants previously further cited Sharko et al. (Alcohol. Clin. Exp. Res. 32: 67-76, 2008) which reported opposite activities of mGluR5 antagonist MPEP and mGluR2/3 antagonist LY341495 in behavioral effects of ethanol in mice. In response, the Examiner asserts that Adams et al. taught the use of mGluR2/3 antagonist to treat addiction, and that Corsi et al. and Chimulera et al. taught the use of a mGluR5 antagonist to treat addiction. The Examiner also quotes *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA) for the proposition that “it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.” The Examiner then asserts that, despite the opposing activities of mGluR5 antagonists and mGluR2/3 antagonists as reported in the art, one would nonetheless be motivated to combine the two treatments for the same addiction.

Applicants cannot agree with the rationale underlying the Examiner’s reasoning. First, mGluR5 antagonists and mGluR2/3 antagonists are known to be targeting different receptors and generate different neurochemical and behavioral responses. Therefore, the administration of these two types of compounds cannot be considered to be “for the very same purpose.” For this reason alone, it would not have been obvious to combine a mGluR2/3 antagonist and a mGluR5 antagonist. In addition, even assuming that antagonizing the two different receptors can be considered the same purpose, the existing overwhelming evidence of their opposing effects would undoubtedly make it non-obvious to combine these two types of compounds. It is illogical and unreasonable to assume that, so long as the art has separately taught treating disease X with compound A and compound B, one would necessarily be motivated to combine the two compounds despite the existence of abundant evidence indicating undesirability or potential side effects of such a combination. By common sense, one would likely be discouraged from even attempting such a combination in light of (1) the known opposite activities of mGluR2/3 and mGluR5 signaling and (2) the lack of therapeutic effect of dual antagonist MCPG as reported in Fundytus et al.

To summarize, the references presented by Applicants clearly indicate that mGluR2/3 and mGluR5 have opposing effects on glutamate signaling as well as the ensuing neurochemical and behavioral responses. Therefore, one would not be motivated to combine antagonism of these two groups of receptors in treating dependence on drugs of abuse. The data cited by the Examiner do not lend any support to the Examiner's position that such a combination would have been obvious. To the contrary, the cited art (e.g., Fundytus et al.) would most likely teach away from the present invention. In addition, in view of the well recognized opposing effects of mGluR2/3 and mGluR5 on glutamate signaling, as well as the data disclosed in Fundytus et al., there could certainly be no reasonable expectation of success in combining a mGluR2/3 antagonist and a mGluR5 antagonist for treating drug dependence. Instead, the very teaching of Fundytus et al. could lead one to believe that the lack of efficacy of mGluR2/3 and mGluR5 dual antagonist MCPG in treating dependence symptoms could be due to the opposite effects of antagonizing both mGluR2/3 and mGluR5. One would reasonably conclude that the combination of a mGluR2/3 mono antagonist and a mGluR5 mono antagonist would similarly be ineffective. Thus, no prima facie case of obviousness could be established for the presently claimed invention.

Furthermore, even assuming for the sake of argument that the alleged prima facie case was properly established, the unexpected results provided by the present invention as well as the teachings of the prior art as clarified by Applicants herein (e.g., teaching away by Fundytus et al.) are sufficient to rebut the prima facie case of obviousness. For example, while the prior art showed that dual mGluR2/3 and mGluR5 antagonist MCPG had no effect in treating withdrawal symptoms in morphine-dependent rats, the subject specification taught that the combination of a mGluR5 antagonist (MPEP) and a mGluR2/3 antagonist (LY341495) was useful to treat established cocaine/nicotine dependence (see, e.g., Figures 14-16 and the discussions of Example 3.5 at page 76). Of particular importance is the finding by the present

inventors that the effect of mGluR2/3 antagonist LY341495 on established nicotine dependence can be potentiated by co-administration of mGluR5 antagonist MPEP at a concentration where MPEP itself had no effect in treating addiction. Specifically, Figure 9C showed that MPEP at a dosage of 1mg/kg had no effect in reducing nicotine or cocaine self-administration in dependent rats. In contrast, as shown in Figures 14-15, such a MPEP dosage was effective in potentiating the inhibitory effects of mGluR2/3 antagonist LY341495 on nicotine self-administration. The additive effects on inhibiting drug-taking behavior as illustrated by these data demonstrate that the combination of a mGluR2/3 antagonist and a mGluR5 antagonist as presently claimed is more effective than each of the two compounds alone in treating addictive disorders. Such an advantageous property of the claimed combination definitely underscores another non-obviousness nature of the present invention.

For all the reasons set forth above, Applicants submit that the presently claimed invention is non-obvious over the cited art. Withdrawal of the instant rejection is therefore respectfully requested.

CONCLUSION

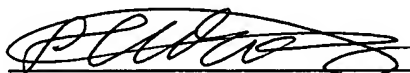
In view of the foregoing, Applicants respectfully submit that the claims now pending in the subject patent application are in condition for allowance, and notification to that effect is earnestly requested. If a telephone conference would expedite prosecution of this application, please telephone the undersigned attorney at 858-784-2937.

The Director is hereby authorized to charge our Deposit Account No. 19-0962 in the event that there are any charges associated with the present Response or any Response in connection with this application.

Respectfully submitted,

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Date



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